Reprinted from the Archives of Environmental Health
June 1972, Volume 24
Copyright 1972, American Medical Association

PB 279 185

PESTICIDE
PUBLICATION

532

Absorption and Excretion of Parathion by Spraymen

Environmental Protection Agency
Athens, Georgia 30341

William F. Durham, PhD. Perrine, Fla; and
Homer R. Wolfe, and Joseph W. Elliott, MS, Wenatchee, Wash

Significant amounts of the urinary metabolite *p*-nitrophenol were detected in the urine of spraymen as long as ten days after last exposure to the organophosphorus insecticide, parathion. Approximately two days after exposure, excretion was insignificant during late night and early morning hours, but reached higher levels during midday. The height of immediate postexposure excretory peaks and the delayed midday rises in excretion seemed to vary directly with the temperature. Bathing after exposure was associated with a rapid decrease in *p*-nitrophenol excretion. Tests considering only one route of exposure at a time indicated that the dermal route represents a potentially greater source of absorption than the respiratory route for orchard spraymen using liquid parathion formulations under the conditions of this study. However, with equivalent absorbed dosages the respiratory route is the more hazardous.

THE organic phosphorus insecticide parathion is a compound of known high acute toxicity to experimental animals. Its use during the more than 20 years since its introduction has resulted, for persons occupationally exposed, in accidental poisonings, some of which have been fatal. The development of effective safety recommendations for workers using parathion and other highly toxic pesticides requires information as to the relative importance of the various possible routes of exposure which might be involved. In those cases of accidental occupational poisoning which occur, it is usually impossible to determine if the exposure was predominantly respiratory or predominantly dermal. However, there is some experimental evidence to indicate that, at least under certain conditions, potential exposure of spraymen to parathion is predominantly by the dermal route. Using the dermal and respiratory exposure pad and air sampling techniques, Batchelor and Walker[1] found that dermal contamination was considerably greater than respiratory contamination for orchard spraymen. Similar results which indicate a preponderance of dermal over respiratory contamination have been obtained for mosquito control spraymen applying malathion or *O*-(3-chloro-4-nitrophenyl) *O*, *O*-dimethyl phosphorothioate (Chlorthion) aerosol[2]; entomologists checking azinphosmethyl or methyl-parathion-treated cotton[3]; orchardists applying sodium salt of dinitro-*o*-cresol (Na-DNOC) as an apple thinning spray[4,5] or DDT[6]; workmen applying the herbicide 2,4-dinitro-*o*-*sec*-butylphenol (DNOSBP)[5]; operators formulating or spraying azinphosmethyl,[7-9] endrin, malathion, parathion, or carbaryl with ground equipment

Submitted for publication Sept 16, 1971; accepted Dec 20.

From the Wenatchee Research Station, Perrine Primate Laboratory, Office of Research and Monitoring, Environmental Protection Agency, Wenatchee, Wash. Mr. Elliott is now with the Salmon Culture Laboratory, Longview, Wash.

Reprint requests to Wenatchee Research Station, Environmental Protection Agency, PO Box 73, Wenatchee, Wash 98801 (Mr. Wolfe).

or endrin by air[8]; workmen applying lindane or DDT to forest land[10]; and vector control spraymen applying dieldrin[11] or DDT.[12]

On the other hand, studies of volunteers have revealed a lack of toxic effect from large dermal doses of parathion,[13] although parathion applied to the skin of laboratory animals has shown high toxicity,[14] and one human case of severe parathion poisoning has resulted from dermal application of the compound in an attempt to relieve pruritus.[15] In the studies on volunteers, the absorption of large amounts of parathion or its breakdown products following dermal dosing was confirmed by the finding of high levels of *p*-nitrophenol in the urine (up to 5.8 mg/24-hr sample), but little or no associated cholinesterase depletion and no cholinergic signs or symptoms occurred. However, the same investigators were able, under other conditions of dosage, particularly by the respiratory route or by a combined respiratory-dermal administered dosage, to produce significant cholinesterase depletion as well as serious poisoning in volunteers.[13,16]

Hartwell and Hayes[16] showed that, if to formulating plant workers or crop-dusting pilots exposed to parathion and mevinphos respiratory protection was provided in the form of pure compressed air for breathing, the measure was effective in preventing poisoning as well as in reducing noncritical exposure as measured by blood cholinesterase activity level.

The oral route of exposure has generally been considered to be of minor significance for workmen using toxic pesticides. However, Quinby et al[17] have described the serious poisoning of a parathion sprayman whose exposure was thought to have occurred from eating a candy bar which he had carried all day in an open pocket during his spray activities. These authors presented comparative curves from poisoning cases which showed that *p*-nitrophenol excretion decreased much more rapidly after oral exposures than after dermal exposures.

The present study, using urinary excretion of *p*-nitrophenol as an indicator, was carried out to obtain additional information on the exposure of spraymen to parathion and particularly, to obtain more information on the relative importance of dermal vs respiratory routes of exposure.

Materials and Methods

Excretion of *p*-Nitrophenol by Spraymen.—Spraymen studied for *p*-nitrophenol excretion included 16 orchardists from the Wenatchee Valley of the state of Washington. These men were operators of power airblast spray equipment, applying 0.33% liquid parathion (1 lb of 25% water-wettable powder per 100 gal of water) formulation to fruit orchards. The study involved 33 spraying days and further observations for an additional 64 days. The men kept a complete record of their activities while participating in the study. The record included the time spent spraying parathion, other work which might involve exposure to parathion, and the bathing schedules of the men. They made complete 24-hour collections of urine for several days during and following their exposure to parathion. Each voiding was kept in a separate container, and the time of excretion was recorded. A total of 514 urine samples was analyzed for *p*-nitrophenol. Samples were analyzed for *p*-nitrophenol content by the method of Elliott et al.[18] Results were calculated as *p*-nitrophenol excretion per hour.

Potential dermal exposure of these spraymen to parathion was estimated using the absorbent pad technique described by Durham and Wolfe.[6] Potential respiratory exposure for the time the worker actually sprayed was calculated by using the mean parathion respiratory exposure of 0.020 mg/hr, which had been determined in earlier studies for spraymen operating airblast equipment.[19] During the actual period of study, respiratory measurement could not be made by this method without severely reducing the respiratory absorption of parathion by the subject. The technique for estimating potential dermal absorption involved placement of pads on clothed body parts which were in close approximation to the bare skin to be studied. Thus, the pad did not significantly influence the total dose received by means of the dermal route.

Comparative Dermal and Respiratory Exposure to Parathion.—In special controlled studies of the comparative dermal and respiratory exposure of workers subjected to the mist emitted from an airblast spray machine during parathion application in orchards, the technique developed at the Phoenix Field Station, National Communicable Disease Center, Public Health Service,[13] was used. In this procedure, one individual was completely covered with rubber and plastic clothing to prevent skin contamination. He breathed ambient air and, thus, had respiratory exposure only. A second worker breathed pure compressed air but wore

ordinary clothing, so that he had dermal exposure only. The third person had neither respiratory nor dermal protection, other than ordinary clothing. The workers wore absorbent pads to provide another measure of their potential, or real, dermal exposure. The three individuals were about equally exposed to a parathion spray drift by transport in a jeep following the spray machine at a distance such that the spray mist was fine enough to remain suspended in the air for a comparatively long period. Exposure to this fine mist, rather than the course droplets encountered near the rear of the spray machine, was similar to that encountered by the operator of such equipment. Urine samples were collected for 24 hours by the three subjects, and the *p*-nitrophenol excretions were determined and compared. Two replicates of this test were carried out.

The Smyth technique, described in detail by Durham and Wolfe,[20] was used to obtain additional values for comparing dermal and respiratory absorption for field spraymen. It involves estimation of total absorption of a chemical from measurement of the chemical or its biotransformation products in the excreta. Respiratory absorption was assumed to be equivalent to respiratory exposure. Respiratory exposure for five subjects was based on mean value for special respirator pads from spraymen exposed under comparable conditions. Respiratory exposure for the sixth subject was based on air concentration of parathion and an assumed tidal volume and respiratory rate. Dermal absorption was calculated by difference between total absorption and estimated respiratory absorption.

Results

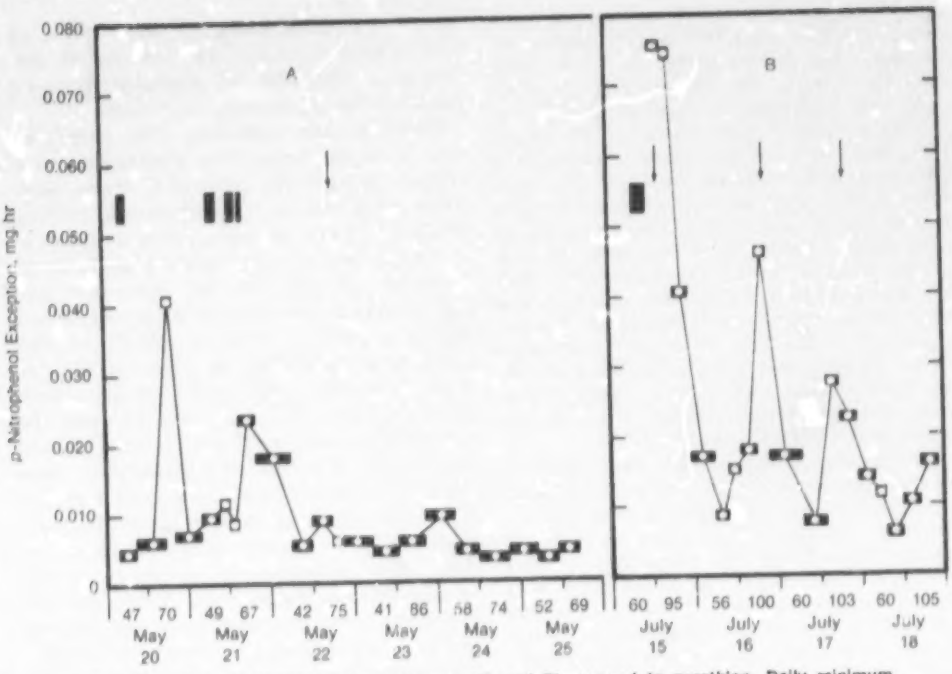
Excretion of *p*-Nitrophenol by Spraymen Exposed to Parathion Under Field Conditions.—The Figure illustrates two examples, from the total of 16 spraymen studied, of excretion of *p*-nitrophenol by two workers exposed to parathion. From a study of these curves, and others not illustrated, a number of conclusions were drawn regarding the relationship between exposure to parathion and excretion of *p*-nitrophenol.

In almost every instance in which a sprayman was studied, there was a significant increase in the excretion of *p*-nitrophenol in association with the exposure period. The highest excretion occurred, on the average, about six hours after the last exposure. However, in some instances, particularly in cases where spraying was prolonged, the highest excretion occurred soon after or even before, exposure was terminated. Excretion of *p*-nitrophenol generally decreased rapidly after the postexposure peak.

Bathing after exposure was associated with a rapid decrease in *p*-nitrophenol excretion. Apparently, removal of excess parathion from the skin by thorough bathing limited further absorption of the insecticide. Although bathing may cause a decrease in *p*-nitrophenol excretion, the spraymen usually bathed in the evening when one would expect a decrease to occur. Of 51 evening baths recorded during the study, all but one were associated with decreases in *p*-nitrophenol output. Decreases also followed the six daytime baths recorded. In many cases, appreciable amounts of *p*-nitrophenol were detected in the urine as long as four or five days after exposure, depending on the magnitude of the exposure. However, about two days after exposure, the excretion of this metabolite was insignificant during the late night and early morning hours, but reached higher levels during the middle of the day. The higher temperature, the greater activity at midday, or both, may have contributed to the more rapid absorption and consequent excretion of parathion during this period. After his period of spraying was completed, each person who was under study was urged to refrain from wearing contaminated clothing and to minimize other exposure to a contaminated environment. In most instances it was impossible to isolate the subject completely from all environmental exposure to parathion, since he usually had to enter the orchard for brief periods to change irrigation sprinklers or to do other tasks. However, in the few instances in which the subject was completely out of all environmental contact with sprays, the diurnal excretion pattern persisted.

The height of immediate postexposure excretory peaks and of the delayed midday rises in excretion also seemed to vary directly with temperature. This variation is most apparent when one compares the hot days of July with the cooler days of May. This observation strengthens the possibility that the diurnal variation noted in the *p*-nitrophenol excretory pattern may be related to diurnal changes in temperature.

None of the *p*-nitrophenol excretion levels



Excretion of p-nitrophenol by two spraymen (A and B) exposed to parathion. Daily minimum and maximum temperatures, in degrees Fahrenheit, shown for each date. Sample period represents interval covered by collection of a voiding of urine (total number of hours per voided specimen). Spray period (solid blocks); bath (arrows); sample period (open circle blocks) as indicated.

of the spraymen studied approached the high values sometimes seen in asymptomatic workers, much less the levels seen in poisoned adults. The highest rate of excretion of *p*-nitrophenol noted in this study was 0.151 mg/hr (2.4 ppm). This value may be compared with the peak level of 3.0 ppm and the mean level of 1.6 ppm for spraymen (part-time ground applicators) reported by Arterberry et al.[21] In general, the spraymen who were included in the present study were careful workers, selected as persons who would keep the accurate records and complete urine samples required. On the whole, they probably paid more attention to safety precautions than the average sprayman.

Comparative Dermal and Respiratory Exposure to Parathion.—As can be seen in Table 1, results were similar in each of the two tests involving measurement of comparative dermal and respiratory exposure of workers under controlled conditions.

In test 1, analysis of dermal exposure pads from right shoulder, left shoulder, back, and chest areas confirmed that all three workers were subjected to spray mist contamination of about the same order of magnitude. The average parathion concentration on the pads was 0.031 mg/sq in for the man wearing the plastic suit, and 0.029 mg/sq in for the man using the pure air supply. The man wearing no protection was subjected to less potential dermal exposure (0.017 mg/sq in) than the other two subjects.

The total *p*-nitrophenol excretion for the man wearing the plastic suit (respiratory exposure only) was 0.088 mg; for the individual using the pure air supply (dermal exposure only), 0.666 mg; and for the man using no special protective equipment (both respiratory and dermal exposure), 0.433 mg.

In test 2, analysis of exposure pads confirmed that total potential spray impingement was about equal for the man wearing the plastic suit (0.020 mg/sq in) and for the man provided with the pure air supply (0.019 mg/sq in). However, the total *p*-nitro-

Table 1.—Potential Skin Contamination and Total p-Nitrophenol Excretion While Wearing Various Protective Equipment Items*

Subject	Protective Equipment	Route of Exposure	Potential Skin Contamination, Parathion, mg/sq in		Total p-Nitrophenol Excretion, mg	
			Test 1	Test 2	Test 1	Test 2
1	Plastic and rubber clothing	Respiratory only	0.031†	0.020†	0.088	0.006
2	Pure air supply	Dermal only	0.029	0.019	0.666	0.497
3	0	Respiratory and dermal	0.017	...	0.433	...

* For workers exposed to parathion spray mist.
† Since this subject's skin was covered by plastic and rubber clothing, he could not absorb any of this potential dosage. Quantity was measured and illustrates similarity in exposure conditions for various subjects.

Table 2.—Calculated Dermal Absorption of Parathion by Workers Spraying Orchards

Subject	Total Urinary Parathion Excretion, mg	Respiratory Exposure			Dermal Exposure			Calculated Dermal Absorption (Excretion Minus Respiratory Exposure)		
		mg/hr	hr	Total, mg	mg/hr	hr	Total, mg	Total, mg	Proportion of Total Excretion, %	Dermal Exposure, %
1	0.67	.020*	6.25	0.13	13.6	6.25	85.0	0.54	80.6	0.63
2	1.50	.020*	7.25	0.15	14.1	7.25	102.2	1.36	90.7	1.33
3	1.49	.020*	7.50	0.15	12.6	7.50	94.5	1.34	89.9	1.41
4	1.36	.020*	7.75	0.16	9.5	7.75	73.6	1.20	88.2	1.63
5	0.51	.020*	5.00	0.10	20.4	5.00	102.0	0.41	80.4	0.40
6	7.91	.055	13.75	0.76	26.9	13.75	369.9	7.15	90.2	1.95
Mean	...	...	...	0.24	...	...	137.9	2.00	86.7†	1.23†

* Mean respiratory exposure for airblast spray equipment operators.
† Based on individual proportions.

enol excretion was 0.006 mg for the for- r (respiratory exposure only) and 0.497 g for the latter (dermal exposure only). A bject with no protective equipment was t included in this test.

The results of these tests indicate that to chard spraymen using liquid parathion rmulations, under the conditions of this udy, the dermal route may represent a eater source of absorption than the re- iratory route. This should not, however, construed to mean that workers should glect respiratory protection where there is piratory exposure because at any given sage rate respiratory exposure is more ngerous, inasmuch as by this route the sticide is more readily and more complete- absorbed.

The data obtained by the application of Smyth technique[20] to exposure and ex- tion studies in field spraymen are presented in Table 2. In each of the spray exposures in this study the calculated dermal absorption was greater than the estimated respiratory absorption. The calculated dermal absorption represented, on the average, 87% of the total absorption. However, the calculated dermal absorption represented only a small percentage (range, 0.40% to 1.95%; mean, 1.23%) of the measured potential dermal exposure.

Comment

The use of *p*-nitrophenol excretion as a measure of absorption of parathion seems to be a valid procedure. The applicability of this measurement to dermal absorption of parathion has been strengthened by the work of Fredriksson et al,[22] who reported that parathion was not hydrolyzed or transformed into paraoxon by the skin of man, cat, rabbit, or rat and by Nabb et al,[23] who

found evidence that parathion, when applied dermally to rabbits, reaches the blood stream largely unaltered. Arterberry and his colleagues[21] have shown that there is a reasonably good correlation between *p*-nitrophenol excretion and exposure to parathion, change in blood cholinesterase activity level, and the occurrence of poisoning. The greater sensitivity of *p*-nitrophenol excretion as compared to blood cholinesterase activity level for measuring exposure to parathion has made possible studies of parathion metabolism at quite low levels of exposure. A particularly sensitive method for detection of *p*-nitrophenol has been developed by Cranmer,[24]

Baetjer and Smith[25] have reported that parathion is more toxic to mice at higher environmental temperatures. The temperature effect was less marked when the parathion was injected intravenously than when it was given intraperitoneally. The authors interpreted this difference as an indication that variation in the rate of absorption was probably the most important factor causing the increased toxicity at higher temperature.

Physicians and others in certain agricultural areas have observed for a long time that poisoning from the organic phosphorous insecticides occurs more often in unusually hot weather than under cooler conditions. However, more spraying is done in the warmer weather; therefore, any valid conclusion, based on epidemiologic data relating to the effect of temperature on poisoning, would have to take into account the intensity of exposure and the size of the population at risk. Our present studies with exposed workers also indicate that, after dermal exposure to parathion, greater excretion of *p*-nitrophenol is associated with higher temperature. This effect was shown not only in connection with diurnal variations but also in connection with seasonal variations in temperature. The seasonal difference in excretion of *p*-nitrophenol tends to discount the importance of muscular work and other activity which might be considered as a factor in the observed diurnal difference in excretion of *p*-nitrophenol. Furthermore, the relationship observed by Funckes et al[26] and by Baetjer and Smith[25] depended on temperature, not on activity.

Diurnal variation in excretion of *p*-nitrophenol has been observed only after dermal exposure to parathion, probably because absorption is relatively prolonged after dermal exposure, as compared with oral exposure.[17]

The studies of dermal absorption of parathion reported above indicate that absorption by this route is both slow and incomplete and that the rate of this absorption is probably increased by higher temperatures. There may be other factors which, under certain circumstances, also may act to increase the rate of dermal absorption. It is generally recognized that injury to the skin may greatly increase its permeability.[27] In addition, there are conditions that may modify the reaction of the host organism to the absorbed toxicant. One of the most commonly recognized conditions is previous exposure to an anticholinesterase compound.

It is of interest to note Fredriksson and Bigelow's study[28] of the tissue distribution of parathion labeled with phosphorus 32 in the mouse, following subcutaneous injection. These workers stated that radioactivity (representing stored parathion) was low, or absent, in the skin among other tissues. However, study of their original slides indicates that appreciable levels of parathion were present in the skin.

The evidence presented here indicates that, under the conditions of this study of orchard spraymen using parathion in an airblast type of spray machine, skin contamination is potentially a more important route of absorption, but not necessarily of poisoning, than the respiratory route. This conclusion may not be valid for other compounds, or even for parathion under different conditions of use. However, the present work does extend the original observation of Batchelor and Walker[1] one additional step. Their work showed that much larger amounts of parathion impinged on the skin than were breathed into the lungs. The results presented here confirm those of Durham and Wolfe[29] and indicate that, even when the more rapid and more nearly complete absorption by the respiratory route is considered, the skin still represents an important route of entry for parathion or its metabolite.

On the basis of these results, precautions for use of parathion should emphasize the importance of protecting the skin from expo-

sure. Spraymen should also be encouraged to use respirators to prevent respiratory absorption.

References

1. Batchelor GS, Walker KC: Health hazards involved in use of parathion in fruit orchards of north central Washington. *Arch Industr Hyg* 10:522-529, 1954.

2. Culver D, Caplan P, Batchelor GS: Studies of human exposure during aerosol application of malathion and chlorthion. *Arch Industr Health* 13:37-50, 1956.

3. Quinby GE, Walker KC, Durham WF: Public health hazards involved in the use of organic phosphorus insecticides in cotton culture in the Delta area of Mississippi. *J Econ Entom* 51:831-838, 1958.

4. Batchelor GS, Walker KC, Elliott JW: Dinitroorthocresol exposure from apple-thinning sprays. *Arch Industr Health* 13:593-596, 1956.

5. Wolfe HR, Durham WF, Batchelor GS: Health hazards of some dinitro-compounds: Effects associated with agricultural usage in Washington state. *Arch Environ Health* 3:468-475, 1961.

6. Durham WF, Wolfe HR: Measurement of the exposure of workers to pesticides. *Bull WHO* 26:75-91, 1962.

7. Jegier Z: Exposure to guthion during spraying and formulating. *Arch Environ Health* 8:565-569, 1964.

8. Jegier Z: Health hazards in insecticide spraying of crops. *Arch Environ Health* 8:670-674, 1964.

9. Wasserman M, Zellermayer L, Gon M: L'etude de la toxicologie des pesticides en climat subtropical: I. L'intensité de l'exposition toxique pendant l'application de pesticides, in *Proceedings of the 14th International Congress on Occupational Health.* Excerpta Medica International Congress series 62, Madrid, Executive Committee of the 14th International Congress on Occupational Health, 1964, pp 1728-1733.

10. Wassermann M, Iliescu S, Mandric G, et al: Toxic hazards during DDT- and BHC-spraying of forests against *Lymantria monàcha*. *Arch Industr Health* 21:503-508, 1960.

11. Fletcher TE, Press JM, Wilson DB: Exposure of spraymen to dieldrin in residual spraying. *Bull WHO* 20:15-25, 1959.

12. Wolfe HR, Walker KC, Elliott JW, et al: Evaluation of the health hazards involved in house-spraying with DDT. *Bull WHO* 20:1-14, 1959.

13. Hayes GR, Funckes AJ, Hartwell WV: Dermal exposure of human volunteers to parathion. *Arch Environ Health* 8:829-833, 1964.

14. Gaines TB: Acute toxicity of pesticides. *Toxic Appl Pharmacol* 14:515-533, 1969.

15. Prinz HJ: Severe percutaneous poisoning with parathion. *Arch Toxik* 25:318-328, 1969.

16. Hartwell WV, Hayes GR Jr: Respiratory exposure to organic phosphorus insecticides. *Arch Environ Health* 11:564-568, 1965.

17. Quinby GE, Loomis TA, Brown HW: Oral occupational parathion poisoning treated with 2-PAM (2-pyridine aldoxime methiodide). *New Eng J Med* 268:639-643, 1963.

18. Elliott JW, Walker KC, Penick AE, et al: Insecticide exposure: A sensitive procedure for urinary *p*-nitrophenol determination as a measure of exposure to parathion. *J Agr Food Chem* 8:111-113, 1960.

19. Wolfe HR, Armstrong JF, Durham WF: Pesticide exposure from concentrate spraying. *Arch Environ Health* 13:340-344, 1966.

20. Durham WF, Wolfe HR: An additional note regarding measurement of the exposure of workers to pesticides. *Bull WHO* 29:279-281, 1963.

21. Arterberry JD, Durham WF, Elliott JW, et al: Exposure to parathion: Measured by blood cholinesterase level and urinary *p*-nitrophenol excretion. *Arch Environ Health* 3:476-485, 1961.

22. Fredriksson T, Farrior WL Jr, Witter RF: Studies on the percutaneous absorption of parathion and paraoxon. *Acta Dermatovener* 41:335-343, 1961.

23. Nabb DP, Stein WJ, Hayes WJ Jr: Rate of skin absorption of parathion and paraoxon. *Arch Environ Health* 12:501-555, 1966.

24. Cranmer MF: Determination of *p*-nitrophenol in human urine. *Bull Environ Contam Toxic* 5:329-332, 1970.

25. Baetjer AM, Smith R: Effect of environmental temperature on reaction of mice to parathion, an anticholinesterase agent. *Amer J Physiol* 186:39-46, 1956.

26. Funckes AJ, Hayes GR, Hartwell WV: Urinary excretion of parasnitrophenol by volunteers following dermal exposure to parathion at different ambient temperatures. *J Agr Food Chem* 11:455-457, 1963.

27. Malkinson FD, Rothman S: Percutaneous absorption, in Jadassohn J (ed): *Normale und pathologische Physiologie der Haut: I. Handbuch der Hautund Geschlechtskrankheiten.* Berlin, Springer-Verlag, 1962, pp 90-156.

28. Fredriksson T, Bigelow JK: Tissue distribution of I^{125}-labeled parathion: Autoradiographic technique. *Arch Environ Health* 2:663-667, 1961.

Printed and Published in the United States of America